

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) 27-10-2014		2. REPORT TYPE Journal Article		3. DATES COVERED (From - To) Oct 2013 – Jan 2014	
4. TITLE AND SUBTITLE Quality Control in Clinical Laboratory Samples				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Maj Paul R Eden, MT (ASCP), PhD, Maj Cordy F Herring III, MT (ASCP), MS				5d. PROJECT NUMBER 7757	
				5e. TASK NUMBER HD	
				5f. WORK UNIT NUMBER 05/H0D1	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) ¹ Molecular Bioeffects Branch, Bioeffects Division, Human Effectiveness Directorate, 711 HPW/RHDJ, Air Force Research Laboratory, Wright Patterson AFB, OH 45433, USA ² 673 rd MDSS, SGSL, Elmendorf AFB, 99506-3702, AK				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Air Force Materiel Command Molecular Bioeffects Branch Bioeffects Division Human Effectiveness Directorate 711th Human Performance Wing Air Force Research Laboratory Wright-Patterson AFB OH 45433-5707				10. SPONSOR/MONITOR'S ACRONYM(S) 711 HPW/RHDJ	
				11. SPONSORING/MONITORING AGENCY REPORT NUMBER	
12. DISTRIBUTION AVAILABILITY STATEMENT Distribution A: Approved for public release					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Quality control (QC) is one of the most important impacts on laboratory testing - it ensures both precision and accuracy of patient sample results. The integrity of quality control samples is important to both management of overall quality as well as meeting requirements of proficiency testing. Addressing QC issues are critical to identification of potential errors with patient results, including reagent matrix effects as well as calibration misalignment of testing function. Maintaining accurate and frequent checks of laboratory sample testing through quality control is vital to ensuring patient testing is done right and produces accurate results for both the patient and physicians. Also, management of matrix effects and calibration misalignment are important aspects to observing shifting L-J charts and adjustments of accuracy over time. Continuous monitoring of quality control testing and capture of biases or trends are important factors to ensure accuracy of patient testing results. As clinical laboratory scientists, our function as managers is as valuable to the patients as our ability to analyze their samples.					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF: U			17. LIMITATION OF ABSTRACT SAR	18. NUMBER OF PAGES 2	19a. NAME OF RESPONSIBLE PERSON P. Eden
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (Include area code) NA

Quality control in clinical laboratory samples

By Maj. Paul R. Eden, MT (ASCP), PhD, and Maj. Cordy F. Herring III, MT(ASCP), CA CLS, MS

Laboratory testing of patient samples can be a complex procedure, depending on clinical analysis, microbiological study, or blood banking testing among other facets of the clinical laboratory. Quality control (QC) is one of the most important impacts on laboratory testing—it ensures both precision and accuracy of patient sample results. The integrity of quality control samples is important to both management of overall quality as well as to meeting requirements of proficiency testing. Addressing QC issues is critical to the identification of potential errors with patient results, including reagent matrix effects as well as calibration misalignment of testing function. Maintaining accurate and frequent checks of laboratory sample testing through quality control is vital to ensuring that patient testing is done right and that it produces accurate results.

When quality control works effectively, it is able to find and correct flaws in the analytical processes of a lab before potentially incorrect patient results are released. According to Ibrahim et al.,¹ failure of QC testing can result from “clerical, methodological, technical, PT materials stability, and random errors.” (Please visit www.mlo-online.com to read references for this article.) By utilizing quality control practices, a laboratory self-regulates its testing and verifies that the results produced are accurate and precise. Clinical labs use management of documentation as well as incorporation of a continuous improvement process to streamline the overall quality control process.

QC samples are expected to be identical and tested identically to patient samples.² The purpose of repeated quality control testing is to validate precision and accuracy of the results of patient sample testing. Precision is the “degree of agreement among repeated measurements of the same characteristic on the same sample,”³ while accuracy is how close results are to what is expected from a test. For example, a glucose quality control reagent is expected to produce results on average of 100 mg/dL. Ten repeats of that same agent produce results of 96, 98, 101, 92, 93, 88, 92, 93, 91, 90, and 98 mg/dL. These results would indicate a low bias result in the instrument.

Other ways of managing quality control include peer testing and alternative monthly review of QC trends. Clinical laboratories are frequently enrolled in clinical laboratory proficiency testing (PT)

programs that are used to validate their testing protocols. These programs, for example those through the College of American Pathologists (CAP), are utilized not only to validate laboratory testing but to validate personnel training and procedures.¹ CAP’s PT program utilizes samples identical to patient samples and not only validates individual laboratories but utilizes peer comparison to generate more accurate ranges for proficiency samples. Periodic review of QC results is a frequent tool for maintaining quality control of patient samples.

Although PT programs are excellent for evaluating QC performance, they can also help laboratory professionals discover issues with reagents even when controls and calibrators seem to be performing well. In early 2014, several laboratories using the same clinical chemistry analyzer failed a CAP PT survey for Hemoglobin A1Cs (HbA1C). Although the peer data showed that these laboratories were precise with each other based on the data generated, CAP reported that these laboratories had failed the survey. Investigation among the laboratories showed that controls were well within established parameters and calibrations were valid. The laboratories queried the analyzer manufacturer and expressed concerns over reagent quality. The company conducted its own internal investigation and discovered that the reagent would cause results to be 0.4% to 1.0% higher than what should be resulted. The company contacted the FDA and issued a technical bulletin alerting laboratories that patient results could be erroneous, even though calibrators and controls worked as intended. The laboratories contacted patient providers and thousands of patients so that patients could be assessed and retested.

One of the most common tools used to track laboratory quality control samples is the Levey-Jennings (L-J) chart. An L-J chart and the Westgard Rules are frequently used to verify trends, biases, or errors in quality controls. The Westgard Rules observe the normal distribution expected and identify standard deviations produced.⁴⁻⁵ Implementing Westgard rules within an L-J chart can identify violation of the rules based on control limits established for the sample tested.

Many laboratories utilize L-J charts for 14- or 30-day reviews of QC testing. While daily identification of QC deviations from normal

ranges ensures accuracy of sample testing, longer-term reviews are more beneficial to diagnose trends and biases in tests which could be missed on a daily basis. An additional use of the L-J chart without quality control samples is to utilize patient samples as their own controls.⁶ By tracking the running averages of the patient results, a laboratorian can identify drift or problems with analyzer function that

Levey-Jennings Chart for SPC Rules Period: 1/1/2014 - 8/31/2014

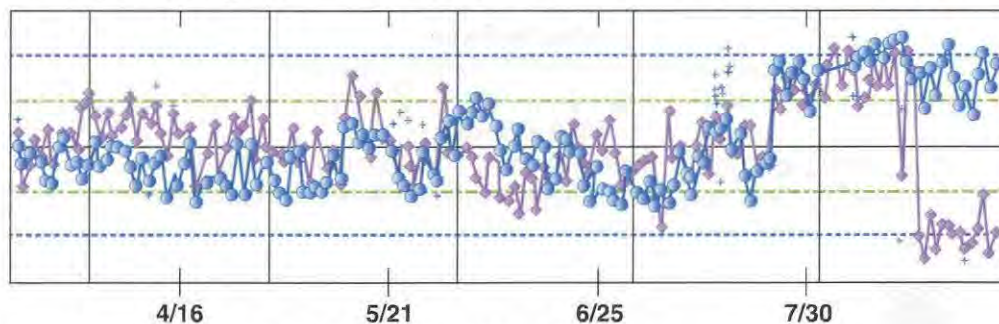


Figure 1. Levey-Jennings Chart for SPC rules—period 1/1/2014-8/31/2014

are not captured by quality control testing. Addressing concerns with QC materials as well as recall issues are common challenges for laboratory managers.

One such concern with QC materials is discovering a "matrix-related bias effect" which can skew normal results. According to Miller et al., "matrix-related bias" [effect] refers to an effect caused by manipulation of the sample matrix during preparation of a QC material that is different from (or in addition to) the naturally occurring differences in matrix among clinical patient samples."⁶ In one laboratory, the Chemistry technical supervisor discovered a matrix-related bias effect with troponin I. Troponin I tests are used for to measure troponin I proteins, which "are released when the heart muscle has been damaged, as in heart attack."⁷ QC for this reagent had been steady for months within a particular accepted range. Data tracking then showed a sudden spike in values for one level of QC and a sudden drop in the other level of QC, even though both sets of QC were within range (**Figure 1**).

The Chemistry technical supervisor contacted the manufacturer and alerted representatives to a possible matrix-related bias effect with third-party materials interacting with the company's reagents. The company investigated the claim and substantiated it. Shortly thereafter, the company issued a technical bulletin advising laboratories to avoid using the third party's QC materials until the bias could be resolved. The laboratory used a different company's QC materials, and values returned to the ranges seen before the matrix effect. The lab leadership was relieved to learn that the bias effect only affected quality control materials and not patient results.

In conclusion, management of quality control can ensure accuracy and precision of both quality and patient results. The focus on trends and biases is a good identification of potential changes in results that can affect accuracy of overall results. Also, management of matrix effects and calibration misalignment are important aspects to observing shifting L-J charts and adjustments of accuracy over time. Continuous monitoring of quality control testing and capture of biases or trends are important to ensure accuracy of patient testing results. As laboratorians, our function as managers is as valuable to the patients as our ability to analyze their samples. □

Maj. Paul R. Eden, USAF, MT(ASCP), PhD, is the Toxicology Program Manager at the 711th Human Performance Wing, Wright-Patterson Air Force Base, OH. His experience includes 18 years in clinical laboratory medicine as well as three years as a research toxicologist. Maj. Cordy F. Herring III, USAF, MT(ASCP), CA CLS, MS, is the Chief of Core Laboratory at the 673d Medical Group, Joint Base Elmendorf Richardson, AK. He has worked and directed in the clinical laboratory for 19 years.



ZeptoMetrix CORPORATION



Leading, Innovating and Developing
Global Solutions for Tomorrow's
Infectious Disease Diagnostics

New  External Run Quality Controls

NATtrol™ *Chlamydia trachomatis* Positive Control Pack - MDZ002
NATtrol™ *Neisseria gonorrhoeae* Positive Control Pack - MDZ003
NATtrol™ CT/NG Negative Control Pack - MDZ004

**From conception to launch,
our Partners and Clients are provided with
cohesive, inventive and cost effective sustainable solutions
and services that consistently exceed even their high standards.**

Product Development

Custom and OEM Research, Design & Development
 Bulk Manufacturing | Component Manufacturing | Custom
 Microorganism Propagation
 Assay Development | In-Process QC Materials
 Proficiency, Validation & Verification Panels
  and RUO Format Availability

Testing Services

Inactivation | Infectivity | Sterility | Stability

Analytical Studies

LOD | Specificity | Cross Reactivity | Interference | Stability
 Assay Precision | Range Validation | Assay Validation & Verification



ZeptoMetrix Corporation
 Corporate Headquarters - 873 Main Street, Buffalo, NY 14202
 Biological Laboratories - Research & Development - 873 Main Street, Buffalo, NY 14202
 Manufacturing, Distribution and Fulfillment - 25 Kenwood Circle, Suite 6, Franklin, MA 02038
 Molecular Diagnostics Division - 25 Kenwood Circle, Suite 9, Franklin, MA 02038
 Customer Relations - 716-882-0920 ph